REMARKS

Claims 1-9 and 11-18 were pending. Claims 10 and 19-36 were withdrawn from consideration as being drawn to a non-elected invention and species. Claims 2-4, 6-7 and 13 have been amended and new claims 37-42 have been added. Accordingly, claims 1-9, 11-18, and 37-42 are being examined.

Claim 2 is amended at the Office's suggestion, to clarify the meaning of the claim. Support for the newly amended claim 2 is found in the originally filed claim 2.

Claim 3 is amended to substitute the word "treating" in place of "inhibiting", with support for the amendment found in the application at page 15, lines 4-13.

Claim 4 is amended to correct the antecedent basis of the word "subject".

Claim 6 is amended to correct a typographical error, wherein the word "monclonal" is corrected to "monoclonal".

Claim 7 is amended to delete the word "a".

Claim 13 is amended to correct the antecedent basis of the phrase "immune system disease".

Claim 17 is supported in the specification as originally filed at page 15, lines 4-13.

New claim 37 is supported in the specification as originally filed at page 14, line 25 to page 15, lines 2; page 20, lines 9-10.

New claim 38 is supported in the specification as originally filed at page 15, lines 4-6;

page 3, lines 1-3, 12-22.

New claim 39 is supported in the specification as originally filed at page 20, line 30 to page 21, line 4; page 22, lines 16-23.

New claim 40 is supported in the specification as originally filed at page 22, line 25 to page 23, line 2.

New Claim 41 is supported in the specification as originally filed at page 15, lines 4-13.

New Claim 42 is supported in the specification as originally filed at page 15, lines 4-13 and page 19, lines 6-19.

No new matter is added in the amended and new claims. Applicants respectfully request entry of the amendments to the claims 2-4, 6-7 and 13 and entry of new claims 37-42.

Applicants' Invention

Applicants' invention is directed to the use of the following three agents to regulate a cell mediated immune response: 1) a first agent that blocks a CD28/CTLA4/B7-mediated signal e.g., soluble CTLA4, 2) a second agent that blocks a CD40/CD154-mediated signal e.g., anti CD154 antibody, and 3) a third agent that blocks an adhesion molecule-mediated interaction e.g., anti-LFA-1 antibody.

Item 1

The Office has entered Applicants' Communication filed in response to an Office Action dated May 19, 2003. The Office indicates that the Communication was filed on July 22, 2003. However, Applicants' respectfully point out that the Communication was timely

filed on July 17, 2003.

The Office acknowledges Applicants' election, with traverse, of Group I directed to soluble CTLA4 as a species of the first agent, anti-CD154 antibody as a species of the second agent, anti-LFA-1 antibody as a species of the third agent and the species of cardiac allografts.

Items 2-3

Applicants are pleased that the requirement for deposit of biological materials under 35 U.S.C. §112, first paragraph, is satisfied for the claimed biological materials.

Item 4

The Office rejects claim 2 under 35 U.S.C. §112, second paragraph, as indefinite. The Office invites the applicant to amend the wording of claim 2 because the Office finds the dependency and wording of the claim confusing and awkward.

Accordingly, applicants have amended claim 2 to clarify the dependency and the wording.

Item 5

The Office rejects claims 1, 2, 5-9 and 11-17 under 35 U.S.C. §112, second paragraph, as indefinite due to their recitation of the word "regulating" which the Office finds ambiguous in nature, direction and degree. The Office suggests that the Applicants amend the claims to recite a specific endpoint such as "inhibiting" to render the claims clear and definite.

With respect to the phrase "regulating," the specification defines the word "regulate" as meaning "to inhibit or stimulate a response," for example "regulating a lymphocyte-mediated immune response" means to inhibit or stimulate a lymphocyte associated immune response" (page 7, lines 1-3).

Applicants respectfully submit that the word "regulating" is definite and distinctly claims the subject matter disclosed in the application. Therefore, Applicants respectfully request the Office reconsider and withdraw its rejection to the word "regulating."

Item 6

Item 6 merely recites 35 U.S.C. §102(e), and does not require a response.

Item 7

Item 7 merely recites 35 U.S.C. §103(a), and does not require a response.

Item 8

The Office rejects claims 1-7, 9 and 12-18 under 35 U.S.C. §102(e) as allegedly anticipated by Digan et al. (US 2002/0142000 A1).

Applicants respectfully disagree with the Office's rejection.

However, the point is moot, since Digen et al. is not prior art under Section 102(e). Section 102(e) generally provides that a pending application for patent will be considered prior art only as of its filing date, if the application is filed by November 29, 2000. If a patent application is filed before November 29, 2000, then it becomes available as prior art only as of its publication date (Public Law 106-113, Sections 4505 and 4508 attached

herewith as Exhibit 1) (MPEP § 706.02(a)).

Digan et al. was filed on January 10, 2000. This date is before November 29, 2000. Accordingly, Digan et al. is available as art only as of its publication date, i.e., October 3, 2002. Digan's publication date is after the filing date of the subject application, and thus is not prior art as to the subject application.

In view of Public Law 106-113, Sections 4505 and 4508 and MPEP § 706.02(a), the rejection is improper and Applicants respectfully request that the rejection to claims 1-7, 9 and 12-18 be withdrawn.

Item 9

The Office rejects claims 1-9 and 12-18 under 35 U.S.C. §103(a) as unpatentable over Blazar et al. (WO 95/34320) in view of Larsen et al. (U.S. Patent No. 5,916,560) and Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science,Cambridge MA, 1996).

Applicants respectfully disagree with the Office's position for the reasons that follow.

The Legal Standard for Obviousness

The burden is on the Office to establish a *prima facie* case of obviousness by showing that the prior art would have suggested the claimed invention to one of ordinary skill in the art, and that one of ordinary skill in the art would reasonably expect that the method suggested by the references would be successful. The Office must provide evidence that both the suggestion to modify the prior art method and the reasonable expectation of success to obtain the claimed invention can be found in the prior art. In addition, the prior art must teach or suggest, alone or in combination, all of the claim limitations.

No evidence has been presented showing that the references cited by the Office, Blazar et al. in view of Larsen et al. and Strom et al., suggest the claimed invention.

Blazar et al. discloses compositions and methods of inhibiting antigen specific T cell responses with two agents, wherein

1 the first agent inhibits CD28/CTLA4/B7 interactions (page 2, last paragraph), and
2 the second agent inhibits an adhesion molecule interaction with its ligand (page 3, lines 11-12).

In one embodiment, Blazar et al. discloses that the first agent can be a soluble CTLA4Ig, and the second agent can be either anti-LFA-1 antibody **or** an anti-gp39 antibody. Blazar teaches that anti-gp39 can be used as an alternative to anti-LFA-1, not as an addition to it (page 7, line 36 to page 8, line 6).

Blazar et al. does not disclose or suggest using a combination of at least three agents (as the Office notes in the outstanding Office Action) as required by the claimed methods.

Larsen et al. teaches compositions and methods of inhibiting an immune response by using a combination of two agents, wherein the first agent blocks the CTLA4/CD28/B7 pathway and the second agent blocks the gp39/CD40 pathway.

Larsen et al. does not teach, or suggest, an anti-LFA-1 antibody to block cellular adhesion molecules.

Strom et al. teaches the use of therapeutic agents to prevent graft rejection wherein the agents are cyclosporine, tacrolimus, corticosteroids, azathioprine, mycophenolate moretil, rapamycin, OKT3 monoclonal antibody which binds CD3 and polyclonal anti-lymphocyte antibodies (Table 36.1; page 454, first column, third paragraph; page 454,

second column, second paragraph).

Strom et al. does not mention (1) agents such as soluble CTLA4 that block the CD28/CTLA4/B7 pathway, (2) agents such as monoclonal antibodies that block the CD40/CD154 pathway, or (3) agents such as monoclonal antibodies that block adhesion molecules. In particular, Strom et al. does not describe or suggest the use of soluble CTLA4, anti-gp39 antibodies **or** anti-LFA-1 antibodies.

The Office stated that it was within the skill in the art to combine the teachings of the primary reference, Blazar et al., in view of the teachings of Larsen et al. and Strom et al. to render the claimed invention obvious.

Applicants disagree.

It is a well established legal principle that the mere fact that the prior art references could be modified would not have made the modification obvious unless the references suggested the desirability of the modification. *In re Laskowski,* 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989). The question is not simply whether the references teach the particular element of the invention, but whether it would suggest the desirability, and thus the obviousness, of making the combination. *Carella v. Starlight Archery,* 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986). There must be some motivation in the references to make the combination. *In re Fine,* 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Additionally, even if there were a suggestion or motivation to combine all elements of the claimed invention in the references cited by the Office, there is no evidence that any modification of the references would have led to a reasonable expectation of success in obtaining the claimed invention.

Blazar et al. does not suggest using a combination of three agents, let alone the specific three agent combination that is being claimed.

In fact, Blazer et al. teaches away from the Applicants' invention because Blazar et al. teaches that anti-gp39 antibody is a substitute for anti-LFA-1 antibody. Blazer never suggested that an anti-gp39 antibody can be combined with anti-LFA-1 antibody for any use, and did not suggest the use of this combination of agents in the claimed methods.

Neither of the remaining references, Larsen et al. or Strom et al., alone or in combination, cures the deficiencies of Blazar et al.

Larsen et al. discloses blocking the CD28/CTLA4/B7 and CD40/CD154 interactions but does not disclose blocking a third interaction, or binding LFA-1 as claimed. Thus, Larsen et al. does not cure the deficiency of Blazer et al.

Moreover, Strom et al. cannot cure the deficiency of Blazer et al. and/or Larsen et al. to render obvious the claimed methods because Strom et al. does not discuss any of the particular agents or pathways being claimed.

Even if, assuming arguendo, the cited references suggest using a combination of at least three agents, none of the references suggest the use of the combination of agents as in the claimed methods (e.g., the combinations of CTLA4Ig, anti-LFA-1 antibody and anti-gp39 antibody), for the reasons discussed above.

In view of the lack of evidence showing that the claimed invention is obvious in view of the cited references, Applicants respectfully request the Office to reconsider and withdraw its rejection of claims 1-9 and 12-18, under 35 U.S.C. §103(a).

Item 10

The Office rejects claims 6, 8 and 11 under 35 U.S.C. §103(a), as unpatentable over Blazar et al. (WO 95/34320), in view of Larsen et al. (U.S. Patent No. 5,916,560) and Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996), and in further view of the known availability of the deposited material used in the claimed invention.

Applicants disagree.

Since Blazar et al., in view of Larsen et al. and Strom et al. do not render obvious the claimed methods for the reasons discussed above, the fact that the reagents of the claimed methods were publicly available does not remedy the deficiencies of the cited references. Applicants are not claiming the agents of the invention but rather the method of using these agents.

Accordingly, the rejection of the claims under 35 U.S.C. §103(a), does not meet the standards of obviousness required by the courts. Applicants request the Office to reconsider and withdraw its rejection of claims 6, 8 and 11 under 35 U.S.C. §103(a).

Item 11

The Office rejects claims 1-9 and 11-18 under 35 U.S.C. §103(a), as unpatentable over Digan et al. (US 2002/0142000 A1), in view of Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996), and the known availability of the deposited material used in the claimed invention.

Applicants respectfully disagree. However, as stated in item 8, above, the point is moot, because Digan et al. is not prior art to the subject application, for the reasons stated above

(See Exhibit 1), and as set forth in response to Item 10.

Applicants request the Office to reconsider and withdraw its rejection of claims 1-9 and 11-18 under 35 U.S.C. §103(a).

Items 12-13

Items 12-13 state that no claims are allowed, and that the Examiner or his supervisor is available to discuss the application.

CONCLUSION

Applicants respectfully request entry and consideration of the above amendments and remarks made in response to the rejections set forth by the Examiner in the November 19, 2003, Office Action. In view of the Applicants' above amendments and responses to the Examiner's rejection of the claims of the subject application, Applicants contend that the subject application, including pending claims 1-9, 11-18 and new claims 37-42, is in condition for allowance. Accordingly, Applicants request issuance of a notice of allowance.

No fee, other than the extension fee of $110.00, is deemed necessary in connection with the filing of this response. If any fee is deemed necessary, the Patent Office is authorized to charge the amount of any such fee to Deposit Account No. 50-0306.

Respectfully submitted,

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